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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,998	01/25/2002	Mark P. Ohan	270/275US	3516

34055 7590 12/21/2006

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EXAMINER	
GHALI, ISIS A D	
ART UNIT	**PAPER NUMBER**
1615	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,998	OHAN ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/06/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/06/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicants' request for RCE, amendment, IDS, all filed 10/06/2006.

Claims 2, 5, 7, and 10-14 have been canceled.

Claims 1, 3, 4, 6, 8 and 9 are pending and included in the prosecution.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/06/2006 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 3-6, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,849,141 ('141) in view of the article "Collagen-Biomaterial for Drug Delivery" by Friess.

US '141 method for preparing formulation comprising collagen, solvent and glucose, said method comprising mixing of the ingredients (abstract). The formulation is cross-linked using UV irradiation or gamma irradiation (col.6, lines 48-50). The formulation is suitable for implantation and can take the shape of sheet-like (col.7, lines 1-5).

The reference does not teach sterilization by gamma irradiation, however, the reference teaches the desire to preserve and stabilize the formulation by adding preservatives and stabilizers (col.7, lines 11-13).

Friess teaches that gamma irradiation is the method of choice to sterilize collagen biomaterials mainly for its high efficacy and accurately controlled dose (page 121 of the article, paragraph 3.5.2).

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide formulation comprising collagen and glucose that is cross-linked by UV radiation, and instead of stabilizing and preserving the formulation using stabilizers or preservatives as disclosed by US '141 the skilled artisan would gamma irradiate the formulation as disclosed by Friess, motivated by the teaching of Friess that gamma radiation is the method of choice to sterilize collagen biomaterials mainly for its high efficacy and accurately controlled dose, with reasonable expectation of having formulation comprising collagen and glucose that is cross-linked with UV radiation and subsequently sterilized efficiently and accurately by gamma irradiation wherein the formulation is stable at storage and sterile when ready to use.

Response to Arguments

5. Applicant's arguments filed 12/27/2006 have been fully considered but they are not persuasive.

Applicants traverse the obviousness rejection by arguing:

- Applicants argue that the Office Action has made no indication whatsoever of where in Friess or in the '141 patent the skilled person would find the urging to combine the two references as asserted by the office action. Action's proffered motivation is nothing more than a mere statement of the benefit conferred by the invention and does not set forth the required showing of motivation but rather applies the benefit of hindsight in combining disjointed references with the benefit of the invention itself as an explicit roadmap.

In response to this argument, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, US '141 teaches UV-irradiating a composition comprising collagen and glucose for the purpose of cross-linking, and γ-irradiating the composition for sterilization, and γ-irradiation is known method for sterilizing medical products as taught by Friess's reference. US '141 desired to preserve the formulation, therefore, one having ordinary skill in the art would have been motivated to sterilize the formulation of US '141 to preserve it and stabilize it, and one having ordinary skill in the art would have used γ-irradiation as disclosed by Friess because Friess teaches that γ-irradiation is the method of choice and most reliable sterilization method for collagen. Furthermore, US '141 used γ-irradiation for cross-linking, and it is expected that γ-irradiation will sterilize the formulation at the same time because killing bacteria is a property of γ-irradiation. Thus, there is motivation to combine the references in the cited references themselves. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include

knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). However, in this case motivation is drawn from the teachings of the cited references as explained above.

- Applicants argue that US '141 does not teach the use of glucose for the purpose of forming glucose derived cross-linked collagen.

In response to this argument, it is argued that claim 1 is directed to composition and claim 6 is directed to method of its making, and the elements of the composition as well as all the steps of making are disclosed by the combined teaching for the references. Glucose is expected to be able to provide glucose derived cross-linked collagen when exposed to UV radiation.

- Applicants argue that US '141 patent teaches a method for preparing a molding material for use in making sustained released formulation. The '141 patent specifically teaches that such a formulation "must be uniform" but that where the "molding material consists of collagen...the molding material cannot exist in the form of a uniform and homogenous solution." (See '141 patent at column 1, lines 32-41). In contrast, the present invention teaches a composition having collagen and sugar material which has been exposed to UV radiation, gamma radiation or both. Such treatment can result in collagen fragmentation, i.e. a formulation that are no necessarily uniform. As such the '141 patent clearly and specifically teaches away from the use of UV radiation or gamma radiation where the exposure to the UV and/or gamma radiation may lead to fragmentation of the collagen molecules.

In response to applicant's argument, applicants' attention is drawn to the scope of the pending claims which are product comprising collagen and sugar that have been exposed to UV and γ-irradiation, and method of its preparation, and US '141 teaches

the element of the products and the method of its production except for sterilization using γ-irradiation that is taught by Friess's reference. The present claim 1 recites "physical form" and not directed to any specific form of the formulation as a whole or specific forms of its individual components. Thus, the argument regarding the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the formulation disclosed by US '141 is uniform in contrast of the formulation of the present invention that is not necessarily uniform and may have fragmented collagen molecules) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). US '141 does not teach away from the use of UV or γ-irradiating, in contrast, US '141 teaches on col.6, lines 47-50, cross-linking using UV irradiation or γ-irradiation, and applicants use UV irradiation for cross-linking, paragraph 0036 of the present specification.

- Applicants argue that the Office Action's reliance on Friess' assertion that gamma irradiation is "a method of choice to sterilize collagen biomaterials mainly for its high efficacy and dose" is out of context and ignores other highly relevant accurately controlled statements from the same paragraph. In fact, Friess merely includes gamma radiation as one sterilization method and specifically acknowledges that "studies on the effect of γ-irradiation on collagen structure clearly indicate chain scission resulting in a fraction of lower molecular weight material" and that "these molecular changes due to γ-sterilization reduce the mechanical strength of collagen." (page 121, paragraph 3.5.2.) Thus, Friess also teaches away from using γ-irradiation on collagen where the strength of the composition is of importance. Furthermore, there is no mention of glucose in combination with collagen anywhere in Friess, and thus no reason for the skilled person to expect that γ-irradiation on such a compound would provide desirable results. Thus, the skilled person would not in fact have a "reasonable expectation

of having formulation comprising collagen and glucose that is cross-linked with UV radiation and subsequently sterilized efficiently and accurately by gamma irradiation" to yield desirable results.

In response to this argument, applicants' attention is directed to the teaching of Friess on paragraph 3.5.2 on page 121, where Friess teaches that γ-irradiation is the method pf choice to sterilize collagen for its high efficacy and high controlled dose, and mentioned chain scission resulting in a fraction of low molecular weight collagen; however, in same paragraph Friess suggested a solution for the problem of fragmentation by formation of additional cross-links, and that suggests what applicants have done. Therefore, Friess does not teach away from the present claims, but suggest the cross-linking and γ-irradiation. With regard to applicants argument that Friess does not teach glucose, the examiner position is that Friess references is relied upon for the solely teaching that γ-irradiation is known effective method for sterilizing collagen. The teaching of cross-linked mixture of collagen and glucose are taught by US '141, and US '141 also teaches γ-irradiation but for different reason. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different

problem. It is not necessary that the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972). Therefor, the combined teaching of US '141 and Friess would have reasonably and successfully resulted into composition comprising collagen and glucose that has been cross-linked by UV irradiation and sterilized by *γ*-irradiation, as applicants have done.

6. Claims 1, 3, 4, 6, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 09-031334 ('334) in view of the article "Physical crosslinking of collagen fibers: Comparison of ultraviolet irradiation and dehydrothermal treatment" by Weadock et al., and the article "Collagen-Biomaterial for Drug Delivery" by Friess.

JP '334 teaches collagen based matrix by reacting collagen with reducing sugar under conditions in which molecules of collagen cross-link with each other (abstract; paragraph 0017). Example of reducing sugar is glucose (paragraph 0029). Resistance to decomposition of collagen can be raised by radiation or irradiation (paragraph 0010). The matrix is sterilized (paragraph 0049).

Although JP '334 teaches raising resistance to decomposition of collagen by radiation or irradiation, JP '3334 does not explicitly teach UV radiation.

Weadock et al. teach that crosslinking of collagen using UV radiation is rapid and easily controlled, and does not introduce toxic product into the material and provides collagen fibers with desirable mechanical properties (page 1373, right column; page 1378, left column under the title summary).

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide collagen based matrix by reacting collagen with glucose under conditions in which molecules of collagen cross-link with each other and raise resistance to decomposition of collagen by radiation or irradiation as disclosed by JP '334, and use UV radiation disclosed by Weadock et al., motivated by the teaching of Weadock et al. that UV radiation is rapid and easily controlled, and does not introduce toxic product into the material and provides collagen fibers with desirable mechanical properties, with reasonable expectation of having collagen based matrix by reacting collagen with glucose under irradiation with safe and non-toxic UV that provides collagen with the desired mechanical properties suitable for specific intended use.

Although JP '334 teaches sterilization of the collagen matrix, it does not explicitly teach sterilization by gamma irradiation.

Friess teaches that gamma irradiation is the method of choice to sterilize collagen biomaterials mainly for its high efficacy and accurately controlled dose (page 121 of the article, paragraph 3.5.2).

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide collagen based matrix by reacting collagen with glucose under irradiation with UV and sterilize the matrix as disclosed by JP '334 combined with Weadock et al., and use gamma irradiation to sterilize the collagen matrix as disclosed by Friess, motivated by the teaching of Friess that gamma radiation is the method of choice to sterilize collagen biomaterials mainly for its high efficacy and accurately controlled dose, with reasonable expectation of having collagen based matrix

by reacting collagen with glucose under irradiation with UV and sterilized efficiently and accurately by gamma irradiation.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis A Ghali
Primary Examiner
Art Unit 1615

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